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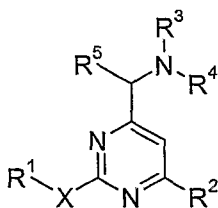
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 4- (SULFANYL-PYRIMIDIN-4-YLMETHYL) -MORPHOLINE DERIVATIVES AND RELATED COMPOUNDS AS GABA RECEPTOR LIGANDS FOR THE TREATMENT OF ANXIETY, DEPRESSION AND EPILEPSY



(I)

(57) Abstract: The present invention relates to compounds of Formula (I) wherein X is -S- or -NH-; R¹ is alkyl, alkenyl, arylalkyl, arylalkenyl or aryl-O-alkyl, wherein the aryl groups are optionally substituted by one or more substituents, selected from the group consisting of lower alkyl, lower alkoxy, halogen or lower halogen-alkyl; R² is hydrogen, lower alkyl or cycloalkyl; R³/R⁴ may form together with the N-atom to which they are attached a non aromatic 5, 6 or 7 membered ring, which may contain in addition to the N-atom one additional heteroatom selected from the group consisting of O, S or N, and wherein the ring is optionally substituted by hydroxy, lower alkyl, lower alkoxy, -NR₂, -CONR₂, -CO-lower alkyl or benzyl; or may form together with the N-atom to which they are attached a heterocyclic ring system, containing at least two rings and which may contain one or two additional

heretoatoms, selected from the group consisting of N or O; R is hydrogen or lower alkyl; R⁵ is hydrogen or lower alkyl; and to pharmaceutically suitable acid addition salts thereof. It has been found that the compounds are active on the GABA_B receptor and therefore useful for the treatment of anxiety, depression, epilepsy, schizophrenia, cognitive disorders, spasticity and skeletal muscle rigidity, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, neuropathic pain and craving associated with cocaine and nicotine, psychosis, panic disorder, posttraumatic stress disorders or gastro-intestinal disorders.



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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference Case 22408	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2005/001814	International filing date (day/month/year) 22/02/2005	(Earliest) Priority Date (day/month/year) 02/03/2004
Applicant F. HOFFMANN-LA ROCHE AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

4- (SULFANYL-PYRIMIDIN-4-YLMETHYL) -MORPHOLINE DERIVATIVES AND RELATED COMPOUNDS
AS GABA RECEPTOR LIGANDS FOR THE TREATMENT OF ANXIETY, DEPRESSION AND EPILEPSY

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

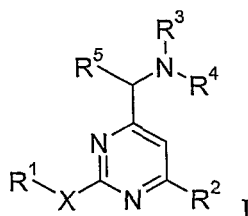
☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

Abstract

The present invention relates to compounds of formula



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wherein

X is -S- or -NH-;

10 R¹ is alkyl, alkenyl, arylalkyl, arylalkenyl or aryl-O-alkyl, wherein the aryl groups are optionally substituted by one or more substituents, selected from the group consisting of lower alkyl, lower alkoxy, halogen or lower halogen-alkyl;

R² is hydrogen, lower alkyl or cycloalkyl;

15 R³/R⁴ may form together with the N-atom to which they are attached a non aromatic 5, 6 or 7 membered ring, which may contain in addition to the N-atom one additional heteroatom selected from the group consisting of O, S or N, and wherein the ring is optionally substituted by hydroxy, lower alkyl, lower alkoxy, -NR₂, -CONR₂, -CO-lower alkyl or benzyl; or may form together with the N-atom to which they are attached a heterocyclic ring system, containing at least two rings and which may contain one or two additional heteroatoms, selected from the group consisting of
20 N or O;

R is hydrogen or lower alkyl;

R⁵ is hydrogen or lower alkyl;

and to pharmaceutically suitable acid addition salts thereof.

25 It has been found that the compounds are active on the GABA_B receptor and therefore useful for the treatment of anxiety, depression, epilepsy, schizophrenia, cognitive disorders, spasticity and skeletal muscle rigidity, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, neuropathic pain and craving associated with cocaine and nicotine, psychosis, panic disorder, posttraumatic stress disorders or gastro-intestinal disorders.

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